REMARKS

Status of the Claims

Claims 1, 3-4 and 7 are pending. Claims 1, 3-4 and 7 are rejected. Claims 1 and 7 are amended herein. Claims 2, 4-6 and 8-22 are canceled. No new matter has been added.

Claim amendments

Claims 1 and 7 have been amended to overcome 35 U.S.C. 112, first and second paragraphs, rejections as discussed *infra*. Claim 1 is amended to incorporate the limitation of a range of high specific activity recited in dependent claim 4. Claim 4 is canceled. Claim 1 is further amended to clarify the relationship between specific activity of the construct, dose of the construct and killing of targeted cells comprising the solid tumor. No new matter is incorporated into the claims by this amendment.

Objection to the claims

Claim 1 is objected to because "a specifically binding sites" is grammatically incorrect. Applicants have amended claim 1 to recite "...binding site on tumor cells comprising the solid tumor".

Miscellaneous

Applicants apologize for the discrepancy between the marked-up and clean versions of claim 1 last submitted. Amendments herein to claim 1 are based on the clean version as the differences are not substantive.

The 35 U.S.C. §112, second paragraph, rejection

Claims 1, 3-4 and 7 are rejected under 35 U.S.C 112, second paragraph, as indefinite for the use of the language "high specific activity" in claim 1 which is a relative term. The term is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. Applicants respectfully traverse this rejection.

Claim 1 is amended to incorporate the limitations of claim 4 to high specific activity ranging from about 0.1 mCi/mg to about 30 mCi/mg. Claim 4 is canceled. Accordingly, in view of this claim amendment, Applicants respectfully request that the rejection

of claims 1, 3-4 and 7 under 35 U.S.C. 112, second paragraph, be withdrawn.

The 35 U.S.C. §112, first paragraph, rejection, new matter

Claims 1, 3-4 and 7 are rejected under 35 U.S.C 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

a. The specification does not disclose a selected value for a high specific activity which is "at least" sufficient for a pharmacologically effective amount of a dose of a construct to provide an amount of antibody to bind to a plurality of target sites on the tumor cell, wherein "at least" one alpha track per tumor cell is delivered thereto from said isotope upon binding of the antibody. Applicants respectfully traverse this rejection.

Applicants have amended claim 1 to define high specific activity as about 0.1 mCi/mg to about 30 mCi/mg. The claim further recites that the specific activity is sufficient for a pharmacologically effective dose of the construct to provide an

amount of antibody to bind to a plurality of targeted sites on the tumor cells wherein a minimum of one atom of said alpha particle-emitting isotope comprising the construct delivers at least one alpha track to the tumor cells upon binding of the antibody. The specification teaches that an alpha emitting antibody will only be effective if a minimum of one atom can be delivered to each cell which results in at least 1 alpha track (Applicants' emphasis) through the cell which requires a high specific activity (pg. 13, ll. 16 to pg. 14, ll. 9). If the alpha-emittor is Ac-225, then one atom will deliver 4 alpha particles as 225-Ac decays with 3 daughters. The specification also teaches that a minimum adequate specific activity of the radioactive construct is an integral characteristic of its description. Without knowing the required specific activity it is not possible for someone skilled in the art to prepare a useful dose adequate to deliver a minimum of 1 atom per cell (pg. 17, ll. 8-11; pg. 26, ll. 5-6).

b. In claim 7 the specification does not disclose the specific dose of 25 mg/m^2. Applicants have amended claim 7 to recite an upper limit of 10 mg/m^2 as disclosed throughout the specification, e.g. Example 15.

Accordingly, in view of these claim amendments and arguments presented *supra*, Applicants respectfully request that the rejection of claims 1, 3-4 and 7 under 35 U.S.C. 112, first paragraph, be withdrawn.

The 35 U.S.C. §112, first paragraph, rejection, scope

Claim 7 is rejected under 35 U.S.C 112, first paragraph, because the specification while being enabling for the method of killing the solid tumor using a construct having a specific activity of about 10 mCi/mg to about 30 mCi/mg, does not reasonably provide enablement for the method of killing the solid tumor with a construct having a specific activity of 0.1 mCi/mg to about 30 mCi/mg. Applicants respectfully traverse this rejection.

The Examiner states that the specification discloses that for a cell line expressing about 10,000 binding sites, e.g., HL60, a minimum specific activity of 10 mCi/mg is needed for a Bi-213 or Bi-212 construct so that at least one alpha particle is tracked through the cells. (pg. 16, ll. 1-13; pg. 36, ll. 3-4). Thus, one cannot extrapolate the teaching in the specification to the claims because as disclosed a minimum specific activity of the construct of 10 mCi/mg

is needed for a cell line expressing 10000 binding sites on its cell surface and because a specific activity of 0.1 mCi/mg is 100 times less than the required 10 mCi/mg. Further it is unpredictable that there exists a tumor cell that has as much as 1,000,000 binding sites in view that the HL 60 cell line expresses only about 10000 binding sites and the SP2/Tac cell line disclosed by Hartman *et al.* only expresses 18, 000 binding sites (Hartman *et al.*, of record, p. 4363, first col., end of first full paragraph). In view of the above, it would require undue experimentation to practice the claimed invention as broadly as claimed.

The instant specification teaches that selecting specific activity requires an understanding of (1) the target site number and (2) modulation and pharmacology of the ligand is required. Site number alone may differ over 1000 fold between different systems (pg. 14, ll. 9-14). The specification further identifies cells having 1000, 10,000 and 1,000,000 binding sites (Table 1). Furthermore, the specification provides an example for calculating a minimum specific activity for Bi-213 or Bi-212 for a cell with 10,000 binding sites of about 10 mCi/mg and extrapolates to other numbers of binding sites (pg. 15, ll. 13 to pg. 17, ll. 5). Example 18 in the

specification teaches that specific activities for Ac-225 constructs of 0.12 mCi/mg and even as low as 0.0012 mCi/mg kill HL60 cells. Thus, for a cell with 10x fewer binding sites than HL60, one of ordinary skill in the art would choose an alpha-emittor appropriate to the target cell, such as Ac-225, to make the labeled construct.

As discussed *supra* and as amended, claim 1 is not drawn solely to a specific alpha-emittor such as Bi-212 or Bi-213, rather one selects an alpha-emittor and a specific activity within a range of about 0.1 mCi/mg to about 30 mCi/mg so that the resultant construct can kill the target tumor cell as described. The specification teaches how to do this and that such method is dependent upon, *inter alia*, number of binding sites on the cell. Thus, it is moot as to whether a cells possessing 1,000,000 binding sites exists or not, although the instant specification does disclose such a cell, because the approximate number of binding sites must be known. The cells have a certain number of binding sites, the known amount of which or estimate thereof is a prerequisite to select an appropriate specific activity. Applicants submit that this would not require an undue amount of experimentation.

Accordingly, in view of these claim amendments and arguments presented *supra*, Applicants respectfully request that the rejection of claims 1, 3-4 and 7 under 35 U.S.C. 112, first paragraph, be withdrawn.

The 35 U.S.C. §103 (a) rejection

Claims 1, 3-4 and 7 remain rejected under 35 U.S.C. §103(a) as being unpatentable over **Simonson** *et al.* (Cancer Res., 50(3 Supp): 9855-9885 (1990)), in view of **Kaspersen** *et al.* (*Nuclear Med Comm*, 16, pp. 468-476 (1995)). Applicants respectfully traverse this rejection.

The Examiner maintains that **Simonson** *et al.* teach:

1. Both single and repeated administration of Bi-212 labeled antibody is utilized wherein a 56% reduction in tumor mass is obtained (p. 986s, first col., third paragraph; Figure 1). The repeated administration taught by **Simonson** *et al.* is not any different from the claimed repeated administration. Further, it is routine in the art to administer a therapeutical agent in multiple doses to increase the effectiveness of treatment.

2. The use of an antibody targeting a cell surface antigen, instead of a secreted antigen, is suggested and treatment of smaller tumor which would have been expected to be even more effective.

3. The specific activity of 5 to 10 mCi/mg taught by **Simonson** *et al.* is certainly within the range of the claimed high specific activity and thus is expected to deliver at least 1 alpha track per cell.

The Examiner maintains that **Kaspersen** *et al.* teach:

4. Bi-213 can be an alternative to Bi-212, being safer and easier to produce than Bi-212.

5. Although **Kaspersen** *et al.* state that Bi-213 may have limited applicability in the treatment of solid tumors but, the Examiner states that **Kaspersen** *et al.* does not teach that Bi-213 cannot be used for treating solid tumors.

Thus, in view of the fact that Bi-212 could be used successfully for treating large solid tumors as taught by **Simonson** *et al.*, and in view of the suggestion by **Kaspersen** *et al.* that Bi-213 can be an alternative to Bi-212, being safer and easier to produce than Bi-212, one of ordinary skill in the art would have expected

that a construct of Bi-213/antibody specific for a solid tumor could be successfully used for treating solid tumors greater than 1 mm in size in diameter.

Applicants' invention is as described *supra*. The Examiner noted that the claims are not drawn to a "cure", rather the claims are drawn to "killing". In the absence of a definition of killing in the specification and for the purpose of compact prosecution, the Examiner has assumed that "killing" refers to killing tumor cells within the tumor. Applicants respectfully draw the Examiner's attention to the statement in the specification defining tumor control probability (TCP); "To achieve a cure (5-year disease-free survival), the probability of killing all tumor cells must approach 1." (pg. 19, ll. 6-7).

Thus, in the instant invention, killing a tumor means reducing the number of tumor cells to 1 to effect a cure or 5 yrs disease-free, as defined. Furthermore, at the time of the instant invention, the specification discloses that "All previously described alpha emitting constructs were of such low specific activity that construction of ligand to their specifications would have yielded ineffective agents or agents unable to induce cures when injected

into humans." (pg. 20, ll. 13-16). The specification further teaches that potency of treatment is critical to effect a cure which requires an alpha-emitting antibody construct having a sufficiently high specific activity designed for the particular tumor cell to be killed.

Simonson *et al.* state that no cures were obtained because a secreted antibody was used and that effectiveness would be better if targeting a cell surface antigen (pg. 987s, second col., first paragraph). This merely acknowledges that alpha particles have a short linear distance and thus are usually more effective when attached to a cell. This does not suggest that cell surface receptor targeting by an alpha-emitting antibody conjugate would effect a cure, only that trying such a method could be more effective and obvious to try is not the standard.

Furthermore, Simonson *et al.* do not even suggest a cell surface antigen that could be targeted. Applicants teach that killing a tumor is dependent on, *inter alia*, the number of binding sites and the high specific activity of the labeled construct. Simonson *et al.* used a Bi-212 labeled construct having specific activity ranging from 5 to 10 mCi/mg. The Examiner states this is within the claimed range and thus a minimum of one alpha would be delivered per cell.

Applicants submit that this depends, *inter alia*, on the number of binding sites on the targeted cells and the binding affinity of the antibody for the antigen, as discussed *supra*, and may be insufficient to form a minimally high specific activity construct. No suggestion is found to use a certain high specific activity and certainly no motivation is present to use a high specific activity antibody construct designed for a specific cell surface antigen because **Simonson** *et al.* do not fairly teach cell surface antigen targeting.

The Examiner's statement that **Simonson** *et al.* suggest that treating a smaller tumor would be expected to be even more effective is a teaching contrary to what is claimed in the instant invention. The instant invention, as claimed, recites killing a solid tumor greater than 1 mm in size. The invention is drawn to killing tumors with potentially increasing diameters and therefore larger. Also, Applicants reiterate that the high specific activity antibody constructs of the instant invention are administered systemically via the vasculature. Simonson *et al.* teach that Bi-212, because of its short half-life, may be appropriate for the treatment of peritoneal disease, e.g., ovarian carcinoma, when administered intraperitoneally (pg. 987s, first col., first paragraph).

In considering **Kaspersen** *et al.*, one of ordinary skill in the art may be motivated to use Bi-213 as an alternative to Bi-212 in that it is safer and easier to produce, but in combining such motivation with the teachings of **Simonson** *et al.* at best one would use a Bi-213 antibody construct with the expectation of results no better than those of Simonson *et al.* because Bi-213 has a shorter half life, i.e., about 46 min. **Simonson** *et al.* teach that the short half life of Bi-212, e.g., about 1 h, limits its use *in vivo*.

Kaspersen *et al.* state that Bi^{-213} may have limited applicability in the treatment of solid tumors (pg. 474, last paragraph). In response, the Examiner states that **Kaspersen** *et al.* does not teach that Bi-213 cannot be used for treating solid tumors. This is certainly true, but given what is fairly taught in **Kaspersen** *et al.* and in Simonson *et al.*, there is no reasonable expectation of success in killing a solid tumor greater than 1 mm in size using either a Bi-212 or Bi-213 antibody construct as taught in **Simonson** *et al.* **Simonson** *et al.* fairly teach that Bi-212 has limited use *in vivo* because it has a short half-life and that in vivo use possibly could be for peritoneal disease via i.p. injection. **Simonson** *et al.* teach effectiveness would be better for smaller rather than larger

peritoneal tumors, particularly before ascites form. **Kaspersen** *et al.* teach that although safer and easier to use, Bi-213 may have limited applicability in treating solid tumors.

Applicants submit that in view of the claim amendments and arguments presented *supra*, **Simonson** *et al.* in combination with **Kaspersen** *et al.* does not render the instant invention obvious. Accordingly, Applicants respectfully request that the rejection of claims 1, 3-4 and 7 under 35 U.S.C. 103(a) be withdrawn.

This is intended to be a complete response to the Final Office Action mailed May 6, 2003. If any issues remain, the Examiner is respectfully requested to telephone the undersigned attorney for immediate resolution. Applicants believe that no fees are due, however, should this be in error, please debit Deposit Account No. 07-1185 on which the undersigned is allowed to draw.

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